Filing Date: October 12, 2000

Title: COMPOUNDS AND METHODS TO ENHANCE rAAV TRANSDUCTION

In the Claims

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Dkt: 875.032US1

Please amend the claims as follows.

- (Previously Presented) A method comprising:
 identifying an agent contacted with a mammalian cell which agent enhances adeno associated virus transduction of the mammalian cell after viral binding to the cell
 membrane and before second strand synthesis which yields an expressible form of the
 viral genome, wherein the agent enhances adeno-associated virus transport to the nucleus.
- 2. (Previously Presented) The method of claim 1 or 87 wherein the cell is a mammalian lung cell.
- 3. (Previously Presented) The method of claim 1 or 87 wherein the cell is a mammalian liver cell.
- 4. (Previously Presented) The method of claim 1 or 87 wherein the cell is a human cell, canine cell, murine cell, rat cell or rabbit cell.
- 5. (Previously Presented) The method of claim 1 or 87 wherein the transduction is enhanced before uncoating of viral particles.
- 6. (Previously Presented) The method of claim 1 or 87 wherein the agent enhances endosomal processing.
- 7. (Previously Presented) The method of claim 1 or 87 wherein the agent is an endosomal protease inhibitor.
- 8. (Original) The method of claim 7 wherein the agent is a cysteine protease inhibitor.

- 9. (Previously Presented) The method of claim 1 or 87 wherein the agent is a peptide or analog thereof.
- 10. (Previously Presented) The method of claim 1 or 87 wherein the virus is recombinant adeno-associated virus.
- 11. (Original) The method of claim 10 wherein the recombinant virus encodes a therapeutic peptide or polypeptide.
- 12. (Previously Presented) The method of claim 10 wherein the recombinant virus comprises a marker gene that is detectable or selectable.

13-28. (Cancelled)

- 29. (Previously Presented) The method of claim 1 or 87 wherein the agent is a compound of formula (I): R₁-A-(B)_n-C wherein R₁ is an N-terminal amino acid blocking group; each A and B is independently an amino acid; C is an amino acid wherein the terminal carboxy group has been replaced by a formyl (CHO) group; and n is 0, 1, 2, or 3; or a pharmaceutically acceptable salt thereof.
- 30. (Original) The method of claim 29 wherein R_1 is (C_1-C_{10}) alkanoyl.
- 31. (Original) The method of claim 29 wherein R_1 is acetyl or benzyloxycarbonyl.
- 32. (Original) The method of claim 29 wherein each A and B is independently alanine, arginine, glycine, isoleucine, leucine, valine, nor-leucine or nor-valine.
- 33. (Original) The method of claim 29 wherein each A and B is isoleucine.

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- 34. (Original) The method of claim 29 wherein C is alanine, arginine, glycine, isoleucine, leucine, valine, nor-leucine or nor-valine, wherein the terminal carboxy group has been replaced by a formyl (CHO) group.
- 35. (Original) The method of claim 29 wherein C is nor-leucine or nor-valine, wherein the terminal carboxy group has been replaced by a formyl (CHO) group.
- 36. (Original) The method of claim 29 wherein R₁ is (C₁-C₁₀)alkanoyl or benzyloxycarbonyl; A and B are each isoleucine; C is nor-leucine or nor-valine, wherein the terminal carboxy group has been replaced by a formyl (CHO) group; and N is 1.
- 37. (Withdrawn) The method of claim 1 or 87 wherein the agent is a compound of formula (II):

$$R_2$$
 R_3
 R_7
 R_8
 R_8
 R_8
 R_8
 R_8
 R_8
 R_8
 R_8
 R_8
 R_8

wherein

R₂ is an N-terminal amino acid blocking group;

 R_3 , R_4 , and R_5 are each independently hydrogen, $(C_1\text{-}C_{10})$ alkyl, aryl or aryl $(C_1\text{-}C_{10})$ alkyl; and

 R_{6} , R_{7} , and R_{8} are each independently hydrogen, $(C_{1}-C_{10})$ alkyl, aryl or aryl $(C_{1}-C_{10})$ alkyl; or a pharmaceutically acceptable salt thereof.

- 38. (Withdrawn) The method of claim 37 wherein R_2 is (C_1-C_{10}) alkanoyl.
- 39. (Withdrawn) The method of claim 37 wherein R₂ is acetyl or benzyloxycarbonyl.

- 40. (Withdrawn) The method of claim 37 wherein R_3 is hydrogen or (C_1-C_{10}) alkyl.
- 41. (Withdrawn) The method of claim 37 wherein R₃ is 2-methylpropyl.
- 42. (Withdrawn) The method of claim 37 wherein R_4 is hydrogen or (C_1-C_{10}) alkyl.
- 43. (Withdrawn) The method of claim 37 wherein R_4 is 2-methylpropyl.
- 44. (Withdrawn) The method of claim 37 wherein R_5 is hydrogen or (C_1-C_{10}) alkyl.
- 45. (Withdrawn) The method of claim 37 wherein R_5 is butyl or propyl.
- 46. (Withdrawn) The method of claim 37 wherein R_2 is acetyl or benzyloxycarbonyl; R_3 and R_4 are each 2-methylpropyl; R_5 is butyl or propyl; and R_6 , R_7 , and R_8 are each independently hydrogen.
- 47. (Withdrawn) The method of claim 1 or 87 wherein the agent is a compound of formula (III):

$$R_{5}$$
 R_{2}
 R_{3}
 R_{4}

wherein

 R_1 is H, halogen, (C_1-C_{10}) alkyl, (C_1-C_{10}) alkenyl, (C_1-C_{10}) alkynyl, (C_1-C_{10}) alkoxy, (C_1-C_{10}) alkanoyl, (=O), (=S), OH, SR, CN, NO₂, trifluoromethyl or (C_1-C_{10}) alkoxy, wherein any alkyl, alkenyl, alkoxy or alkanoyl may optionally be substituted with one or more halogen, OH, SH, CN, NO₂, trifluoromethyl, NRR or SR, wherein each R is independently H or (C_1-C_{10}) alkyl;

thereof.

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 R_2 is (=0) or (=S);

 R_3 is H, (C_1-C_{10}) alkyl, (C_1-C_{10}) alkenyl, (C_1-C_{10}) alkynyl, (C_1-C_{10}) alkoxy or (C_3-C_{10}) C₈)cycloalkyl, wherein any alkyl, alkenyl, alkynyl, alkoxy or cycloalkyl may optionally be substituted with one or more halogen, OH, CN, NO₂, trifluoromethyl, SR, or NRR, wherein each R is independently H or (C_1-C_{10}) alkyl;

 R_4 is H, (C_1-C_{10}) alkyl, (C_1-C_{10}) alkenyl, (C_1-C_{10}) alkynyl, (C_1-C_{10}) alkoxy or (C_3-C_{10}) C₈)cycloalkyl, wherein any alkyl, alkenyl, alkynyl, alkoxy or cycloalkyl may optionally be substituted with one or more halogen, OH, CN, NO₂, trifluoromethyl, SR, or NRR, wherein each R is independently H or (C_1-C_{10}) alkyl;

R₅ is H, halogen, (C_1-C_{10}) alkyl, (C_1-C_{10}) alkenyl, (C_1-C_{10}) alkynyl, (C_1-C_{10}) alkoxy, (C_1-C_{10}) C₁₀)alkanoyl, (=O), (=S), OH, SR, CN, NO₂ or trifluoromethyl, wherein any alkyl, alkenyl, alkynyl, alkoxy or alkanoyl may optionally be substituted with one or more halogen, OH, SH, CN, NO₂, trifluoromethyl, NRR or SR, wherein each R is independently H or (C₁-C₁₀)alkyl; and X is O, S or NR wherein R is H or (C₁-C₁₀)alkyl, or a pharmaceutically acceptable salt

- (Withdrawn) The method of claim 47 wherein R₁ is halogen, CN, NO₂, trifluoromethyl or 48. OH.
- (Withdrawn) The method of claim 47 wherein R_1 is OH. 49.
- (Withdrawn) The method of claim 47 wherein R_2 is (=0). 50.
- (Withdrawn) The method of claim 47 wherein R_3 is H or (C_1-C_{10}) alkyl. 51.
- (Withdrawn) The method of claim 47 wherein R₃ is methyl. 52.
- (Withdrawn) The method of claim 47 wherein R_4 is H or (C_1-C_{10}) alkyl. 53.
- (Withdrawn) The method of claim 47 wherein R₄ is H. 54.

- 55. (Withdrawn) The method of claim 47 wherein R₅ is halogen, CN, NO₂, trifluoromethyl or OH.
- 56. (Withdrawn) The method of claim 47 wherein R_5 is OH.
- 57. (Withdrawn) The method of claim 47 wherein X is O or S.
- 58. (Withdrawn) The method of claim 47 wherein X is O.
- 59. (Withdrawn) The method of claim 47 wherein both ---- are a single bond.
- 60. (Withdrawn) The method of claim 47 wherein one ---- is a double bond.
- 61. (Withdrawn) The method of claim 47 wherein both ----- are a double bond.
- 62. (Withdrawn) The method of claim 45 wherein R₁ is OH, R₂ is (=O), R₃ is methyl, R₄ is H, R₅ is OH, X is O, and both ----- are a double bond.
- 63. (Withdrawn) The method of claim 47 wherein the compound is a compound of formula (III):

$$R_{5}$$
 III

64. (Withdrawn) The method of claim 63 wherein R₁ is halogen, CN, NO₂, trifluoromethyl or OH.

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- 65. (Withdrawn) The method of claim 63 wherein R₁ is OH.
- 66. (Withdrawn) The method of claim 63 wherein R_2 is (=0).
- 67. (Withdrawn) The method of claim 63 wherein R_3 is H or (C_1-C_{10}) alkyl.
- 68. (Withdrawn) The method of claim 63 wherein R_3 is methyl.
- 69. (Withdrawn) The method of claim 63 wherein R_4 is H or (C_1-C_{10}) alkyl.
- 70. (Withdrawn) The method of claim 63 wherein R₄ is H.
- 71. (Withdrawn) The method of claim 63 wherein R₅ is halogen, CN, NO₂, trifluoromethyl or OH.
- 72. (Withdrawn) The method of claim 63 wherein R_5 is OH.
- 73. (Withdrawn) The method of claim 63 wherein X is O or S.
- 74. (Withdrawn) The method of claim 63 wherein X is O.
- 75. (Withdrawn) The method of claim 63 wherein both ---- are a single bond.
- 76. (Withdrawn) The method of claim 63 wherein one ---- is a double bond.
- 77. (Withdrawn) The method of claim 63 wherein both ---- are a double bond.
- 78. (Withdrawn) The method of claim 63 wherein R_1 is OH, R_2 is (=0), R_3 is methyl, R_4 is H, R_5 is OH, X is O, and both ----- are a double bond.

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79. (Withdrawn) The method of claim 1 or 87 wherein the agent inhibits the activation of ubiquitin, the transfer of ubiquitin to the ubiquitin carrier protein, ubiquitin ligase, or a combination thereof.

- 80. (Withdrawn) The method of claim 1 or 87 wherein the agent inhibits ubiquitin ligase.
- 81. (Withdrawn) The method of claim 1 or 87 wherein the agent is a compound of formula (IV):

$$R \longrightarrow A \longrightarrow A_1 \longrightarrow R_1$$

wherein R is hydrogen, an amino acid, or a peptide, wherein the N-terminus amino acid can optionally be protected at the amino group with acetyl, acyl, trifluoroacetyl, or benzyloxycarbonyl; A is an amino acid or a direct bond; A_1 is an amino acid; and R_1 is hydroxy or an amino acid, wherein the C-terminus amino acid can optionally be protected at the carboxy group with (C_1-C_6) alkyl, phenyl, benzyl ester or amide (e.g., $C(=O)NR_2$, wherein each R is independently hydrogen or (C_1-C_6) alkyl); or a pharmaceutically acceptable salt thereof.

- 82. (Withdrawn) The method of claim 81 wherein the agent is H-Leu-Ala-OH, H-His-Ala-OH, or a combination thereof.
- 83. (Previously Presented) The method of claim 1 or 87 further comprising administering a second agent that enhances the activity of the agent.
- 84. (Original) The method of claim 83 wherein the second agent is EGTA.
- 85. (Canceled)
- 86. (Previously Presented) The method of claim 1 or 87 wherein the agent alters endosomal processing.

Serial Number: 09/689,136

Filing Date: October 12, 2000

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- 87. (Previously Presented) A method to identify an agent that enhances adeno-associated virus (AAV) transduction of a mammalian cell, comprising:
 - a) contacting the mammalian cell with one or more agents and adeno-associated virus; and
 - b) identifying at least one agent that enhances transduction after viral binding to the cell membrane and before second strand synthesis which yields an expressible form of the viral genome, wherein the agent enhances adeno-associated virus transport to the nucleus of the mammalian cell.
- 88. (Currently Amended) A method comprising: identifying an agent contacted with a mammalian cell which enhances <u>internalized</u> adeno-associated virus transport to the nucleus.
- 89. (Currently Amended) A method to identify an agent that enhances adeno-associated virus transduction of a mammalian cell, comprising:
 - a) contacting the mammalian cell with one or more agents and adeno-associated virus; and
 - b) identifying at least one agent that enhances <u>internalized</u> adeno-associated virus transport to the nucleus of the mammalian cell.